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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Applicant(s):	Petersen et al.	
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Art Unit:	1651	
Examiner:	Witz, Jean C.	
Title:	BONE GRAFT SUBSTITUTE COMPOSITION	

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APPEAL BRIEF UNDER 37 CFR § 1.192

This Appeal Brief is filed pursuant to the "Notice of Appeal to the Board of Patent Appeals and Interferences" filed March 11, 2005.

1. ***Real Party in Interest***

The real party in interest in this appeal is Wright Medical Technology, Inc., the assignee of the above-referenced patent application.

2. ***Related Appeals and Interferences***

There are no related appeals and/or interferences involving this application or its claimed subject matter. For the sake of complete disclosure, however, it is noted that two of the references cited by the examiner are also relied upon in final rejections of the pending claims of U.S. Appl. No. 09/947,833, filed September 6, 2001, and U.S. Appl. No. 10/060,697, filed January 30, 2002. An appeal brief was filed in these unrelated applications on December 3, 2004 and December 15, 2004, respectively.

3. ***Status of Claims***

Claims 2, 3, 12-21, and 35-38 are pending and all claims stand rejected as unpatentable over a combination of three prior art references as set forth in greater detail below. The prior art rejection of all pending claims is appealed herein.

4. ***Status of Amendments***

All claim amendments presented during prosecution were entered and are set forth in the clean copy of the pending claims appended to the brief. Claims 2 and 12 have been amended twice during prosecution and Claim 3 was amended once. Claims 13-21 and 35-38 were added during prosecution.

5. ***Summary of Claimed Subject Matter***

The present invention is directed to a bone graft substitute composition comprising a calcium sulfate material such as calcium sulfate hemihydrate, demineralized bone, a cellulose derivative such as carboxymethylcellulose, and a mixing solution such as sterile water, as embodied in independent Claims 2 and 12. The invention also includes a method of making a bone graft substitute composition as set forth in independent Claim 35.

Calcium sulfate in its hemihydrate form is known to chemically react with water to form a hardened material (i.e., to set over time). Applicants have discovered that a cellulose derivative as described in the application serves to disrupt the reaction of calcium sulfate hemihydrate into the hardened dihydrate form, thereby increasing the time it takes for the calcium sulfate to form a hardened bone graft composition or completely eliminating the ability of the composition to harden or set. Thus, the present invention provides bone graft compositions that retain a degree of moldability or ejectability for a longer period of time than would be possible with prior art calcium sulfate compositions. In turn, the longer set time provides the clinician with additional time to form the putty or paste into the desired shape matching the bone defect, or additional time to inject the solution using a syringe. The extended set times of embodiments of the invention are discussed, for example, on page 4 of the specification (lines 8-23). Additionally, even in embodiments where the calcium sulfate of the

composition is present in a less reactive form, the addition of the cellulose derivative can impart beneficial handling characteristics, such as improved cohesiveness of the composition, which lessens the tendency of the composition to fall apart when contacted with fluids, and overall better moldability. The beneficial handling characteristics of embodiments of the invention are discussed, for example, on page 4 (lines 1-4) and in the description of each of the "Preferred Embodiments" on pages 6-10, where definitions of handability, ejectability, and robustness are provided.

Independent Claim 2 is directed to a bone graft substitute composition, comprising calcium sulfate, demineralized bone, a cellulose derivative, and a mixing solution. The calcium sulfate ingredient is discussed throughout the specification, such as on page 4 (line 18) and in the first paragraph of each "Preferred Embodiment" description on pages 6-10. The demineralized bone ingredient is discussed, for example, on page 5 (line 22) and in the first paragraph describing the first "Preferred Embodiment" on page 6 (lines 14-15). The cellulose derivative ingredient is discussed, for example, on page 4 (line 19) and page 5 (lines 7-10). Carboxymethylcellulose is mentioned in the first paragraph of each "Preferred Embodiment" on pages 6-10. Mixing solutions are discussed, for example, on page 4 (line 18) and page 5 (lines 4-7). Various specific embodiments of bone graft substitute compositions encompassed by Claim 2 are set forth on page 5 (lines 12-21).

Independent Claim 12 is directed to a bone graft substitute composition where the relative concentrations are also set forth, the composition comprising about 80 to about 120 parts by weight of medical grade calcium sulfate hemihydrate; about 10 to about 100 parts by weight of demineralized bone matrix; about 1 to about 40 parts by weight of a carboxymethylcellulose; and about 21 to about 250 parts by weight of sterile water. Express support for Claim 12 can be found, for example, on page 9 of the specification (lines 1-6). The sections identified above in the discussion of Claim 2 are also believed to be pertinent to the subject matter of Claim 12.

Independent Claim 35 is directed to a method of making a bone graft substitute composition comprising providing a first composition that comprises calcium sulfate, a cellulose derivative, and demineralized bone matrix, and contacting the first composition with a mixing solution to form the final composition. Sections of the specification pertinent to each claimed composition ingredient are set forth above in connection with the discussion of Claim 2. The

claimed method steps are noted, for example, in the second paragraph under each "Preferred Embodiment" section on pages 6-10.

6. ***Grounds of Rejection to be Reviewed on Appeal***

Claims 2, 3, 12-21, and 35-38 stand rejected under 35 U.S.C. §103(a) as being unpatentable over the combined teachings of U.S. Patent No. 5,484,601 to O'Leary *et al.*, U.S. Patent No. 5,385,887 to Yim *et al.*, and U.S. Pat. No. 6,030,635 to Gertzman et al. The Office Action relies upon the O'Leary reference as teaching a composition comprising demineralized bone powder, an organic liquid carrier and, optionally, a thickening agent such as a cellulosic ester. The Office Action relies upon the Yim reference as disclosing a composition for delivering osteogenic proteins that contains calcium sulfate hemihydrate. The Examiner has taken the position that it would have been obvious to include the calcium sulfate taught in Yim in the composition described in O'Leary because both patents are directed to bone growth promoting compositions and Yim teaches that calcium sulfate improves handling, moldability, and consistency in such a composition. The Examiner relies upon the Gertzman reference as disclosing that it is well known to include autologous bone, allograft bone, bone marrow, and blood in bone graft compositions.

7. ***Argument***

Each argument against the sole prior art rejection of record is set forth below.

There is No Motivation to Combine Yim with O'Leary

Applicants respectfully submit that one of ordinary skill in the art would have no motivation to combine the three references of the rejection in the manner contemplated by the Examiner. Specifically, there is no motivation to combine the calcium sulfate hemihydrate of Yim with the teachings of O'Leary.

The O'Leary reference is directed to a flowable demineralized bone powder composition comprising demineralized bone powder in an organic liquid carrier, such as glycerol. It is clear that this reference is directed to compositions that are intended to maintain a certain consistency for an extended period of time. Although this consistency is described as widely varying, there

is nothing in O'Leary to indicate that a composition that hardens or sets over time is envisioned. In fact, the reference suggests otherwise by describing the term "flowable" as including compositions with consistencies ranging from those that are "shape sustaining but readily deformable . . . to those which are runny" (column 3, lines 30-34). Further, we note that O'Leary suggests the use of a thickener if settling of the bone powder within the organic liquid is a problem. (column 3, lines 56-63). This also suggests that the composition is intended to maintain a liquid, flowable state for an extended period of time. Obviously, if the composition is intended to set into a hardened mass within a short period of time, settling would not be an issue. Additionally, the O'Leary reference suggests that the composition described therein can be prepared "well in advance and stored under sterile conditions until required for use" (column 4, lines 34-37; See also, column 1, lines 63-66). This also suggests that the flowable compositions envisioned by O'Leary maintain a uniform flowable consistency for an extended period of time.

All of the above teachings of O'Leary are manifestly inconsistent with the well-known properties of calcium sulfate hemihydrate solutions. As described in the references discussed in the background section of the present application, prior to Applicants' present invention, calcium sulfate hemihydrate was used in certain bone graft compositions where it was understood that the composition would harden or set rather quickly as the calcium sulfate hemihydrate reacted with water to form the dihydrate form. Since it was known in the art that calcium sulfate hemihydrate would cause a composition to harden or set in a relatively short period of time, such as 5-10 minutes, the addition of calcium sulfate hemihydrate to the O'Leary composition would have been avoided by one of skill in the art since the resulting composition would not have been expected to maintain a flowable state for an extended period of time, which is clearly the aim of the reference. Yim itself describes how quickly a calcium sulfate hemihydrate solution loses flowability in Table 2 in column 10. Note that each tested composition appearing in Table 2 was non-flowable within 15 minutes. Better evidence against the combination of O'Leary and Yim could hardly be imagined.

Although Applicants have discovered that the claimed plasticizing substance can forestall the calcium sulfate hemihydrate hardening reaction, this effect is not appreciated in the prior art of bone graft substitute compositions. Yim purports to suggest compositions including both calcium sulfate hemihydrate and certain cellulosic materials that are described as protein

sequestering agents. However, this combination does not appear in any examples and the Yim reference obviously does not appreciate the handling advantages that Applicants have discovered since the reference consistently describes the calcium sulfate hemihydrate as a material that will reduce set-up time and describes numerous compositions in Table 2 that quickly harden or set. As a result, one of ordinary skill in the art without the benefit of Applicants' disclosure would view the combination of calcium sulfate hemihydrate with the O'Leary formulation as likely to negate the flowability requirement set forth in O'Leary. Thus, for this reason, one of ordinary skill in the art would not find the requisite motivation to combine the calcium sulfate hemihydrate of Yim with the O'Leary composition.

Even ignoring the clear suggestion in the art to avoid combining calcium sulfate hemihydrate with O'Leary as discussed above, the Examiner's reasoning for combining Yim with O'Leary is inconsistent with the teachings of the Yim reference. As explained in the after-final office action response, Yim describes the use of calcium sulfate to reduce the preparation time or "set up time" of a composition comprising osteogenic proteins, autogenous blood and a porous particulate polymer matrix material. (column 2, lines 51-65). Presumably, calcium sulfate is useful in this composition to reduce setup time because of the relatively long period of time it takes for autogenous blood to clot in the formulation. Applicants note that this teaching is directly contrary to the present invention since the stated goal in Yim is to reduce set up time, not increase it.

The Examiner relies on language in the Yim reference regarding reduction in set-up time and improvement in handling, moldability and consistency as evidence of a motivation to combine the calcium sulfate hemihydrate of Yim with the formulation of O'Leary. However, as noted above, Yim does not provide a general suggestion that calcium sulfate provides such advantages in all bone graft compositions. Instead, the Yim reference only suggests that a calcium sulfate hemihydrate-containing substance (CSHS) provides such advantages when combined with the formulation described in U.S. Pat. No. 5,171,579 (see column 2, lines 51-65). Yim only suggests a CSHS provides such advantages in the context of a formulation comprising osteogenic proteins, autogenous blood, and a porous particulate polymer matrix, such as a copolymer of lactic acid and glycolic acid (PLGA). There is no suggestion in the Yim reference that such improved properties would be expected in any other formulation. Yim merely teaches

that, "[t]o reduce the preparation time and improve the above formulation's handling characteristics" (emphasis added), a CSHS can be added. The "above formulation" is the formulation described in the '579 patent, which includes an osteogenic protein, autogenous blood, and a porous particulate polymer matrix. Since the composition in the O'Leary reference is not a combination of osteogenic proteins with autogenous blood and a porous particulate polymer matrix such as PLGA, there would be no motivation to combine the CSHS of Yim with the composition described in O'Leary for the reasons suggested by the Examiner. The O'Leary formulation comprises demineralized bone powder and an organic liquid, and such a composition is markedly dissimilar to the composition described in Yim as needing improvement in set-up time, moldability, etc. Further, there is nothing in the O'Leary reference to suggest a problem with moldability, consistency, etc. of the formulation described therein that might lead one of ordinary skill in the art to seek an additive to address such a problem. Indeed, the O'Leary patent seems to suggest that the consistency of the "flowable" material can be adjusted simply by altering the amount of the liquid component (column 3, lines 28-35).

The Examiner responded to this argument in the Advisory Action by noting that Yim describes the addition of calcium sulfate hemihydrate to other compositions as well, such as the suggestion at column 2, lines 27-31 to form a composition containing calcium sulfate hemihydrate and an osteogenic protein. Yet, the Examiner continues to rely on the improved handling/moldability teaching in Yim as the motivating factor for the alleged combination. The Yim reference does not teach that improved handling/moldability will be realized in the other embodiment noted by the Examiner. The osteogenic protein/calcium sulfate hemihydrate embodiment is described more fully at column 8, lines 16-28, where the reference teaches that, in that embodiment, calcium sulfate hemihydrate provides a structural matrix function, an osteoconductive matrix and a protein sequestering function. There is no discussion of improved handling whatsoever. As Applicants have pointed out, the broad statement by the Examiner in the Advisory Action that "Yim shows that bone repair compositions that do not contain [calcium sulfate hemihydrate] will have improved moldability upon the inclusion of the [calcium sulfate hemihydrate]..." is overbroad and unsupported by the Yim reference. Thus, even ignoring the disincentive to use calcium sulfate hemihydrate in the O'Leary reference described above, the

Yim reference fails to provide proper motivation to modify O'Leary in the manner contemplated by the rejection.

The Examiner also stated in the Advisory Action that nonobviousness cannot by shown by attacking references individually where the rejection is based on a combination of references, citing two court cases. However, the cited court cases, *In re Keller* and *In re Merck*, merely note that one must consider the teachings of the cited references as a whole when considering obviousness. One must necessarily consider the teachings of each reference to understand the teachings of the combination, and Applicants have not solely focused on the teachings of O'Leary. Rather, Applicants have argued both that O'Leary teaches away from the combination relied upon by the Examiner, and that Yim fails to provide the requisite motivation. In short, Applicants are not "attacking references individually" but are instead describing the combined teachings of the two references.

The Examiner also suggest that Applicants' use of the term "extended period of time" to describe the ability of the O'Leary formulation to maintain a uniform consistency is "not supported" by the O'Leary patent. While it is obvious that an "extended" period of time is not defined in the O'Leary reference, it is equally apparent that extended periods of time are envisioned in the reference. There is no burden on Applicants to find a quantifiable definition of "extended" in order to overcome the rejection of record. The point of Applicants' argument is that one of ordinary skill in the art would view O'Leary as teaching a composition that maintains a uniform consistency. This must be the case since O'Leary teaches that the bone powder composition taught therein can be prepared "well in advance" and stored in, for example, "the barrel of a syringe or other suitable applicator device" (column 4, lines 34-37). One of ordinary skill in the art would not have considered a calcium sulfate hemihydrate-containing composition as capable of such a use, and even Yim supports the understanding that calcium sulfate hemihydrate causes a composition to lose flowability within minutes, which is certainly not conducive to storage in a syringe for future application.

Further, the Examiner appears to rebut Applicants' argument by noting that the ingrowth of bone tissue at the site of a bone graft leads to hardening in the area. This is simply irrelevant. The hardening at that point is due to tissue growth, not the bone graft composition. The knitting of bone at the site of a wound is immaterial to the characteristics of the O'Leary formulation.

The Examiner also argues that Applicants "appear to be suggesting that O'Leary must identify a problem" in order to be used in an obviousness rejection. Applicants made no such suggestion. However, Applicants do suggest that one cannot ignore the teachings of a reference that lead away from the suggested combination.

For the reasons set forth above, Applicants respectfully submit that neither O'Leary nor Yim provide the requisite motivation to combine the two references as contemplated by the Examiner. In fact, the O'Leary reference teaches away from such a combination. Thus, Applicants respectfully request that the Board overturn the sole rejection or record.

There is No Motivation to Combine Gertzman with O'Leary

In addition, Applicants respectfully submit that there is no motivation to combine the teachings of the Gertzman reference with the teachings of O'Leary. The composition described in the Gertzman reference is so fundamentally distinct from the composition described in the O'Leary reference that one of ordinary skill in the art would view such differences as weighing against the combination suggested by the Examiner.

The Gertzman reference is directed to a malleable paste for filling bone defects, the composition including a high molecular weight hydrogel and an aqueous solution as the carrier for demineralized bone powder. The O'Leary reference is clearly not directed to compositions including a high molecular weight hydrogel component as a carrier ingredient for demineralized bone, and for this reason, one of ordinary skill in the art would not view the teachings of Gertzman as relevant to the O'Leary composition.

Further, the Gertzman reference specifically contrasts the teachings of the O'Leary reference. In the background section, the Gertzman reference points out numerous disadvantages associated with GRAFTON, a commercial embodiment of the composition of O'Leary. For instance, Gertzman notes that the glycerol carrier of GRAFTON has a very low molecular weight and low viscosity at higher temperature, which contribute to making the composition "runny" when used in surgery. The Gertzman reference notes that one method of overcoming this negative characteristic of GRAFTON is to use larger bone particles. However, the use of larger bone particles is less preferred for a variety of reasons mentioned in Gertzman. Additionally, Gertzman suggests "glycerol and other similar low molecular weight organic

solvents are toxic and irritating" (column 3, lines 22-23). The Gertzman reference clearly indicates that the composition described therein is intended to overcome the deficiencies of GRAFTON and similar compositions, such as the compositions described in O'Leary. Gertzman et al. expressly note that their composition "avoids the toxic problems ... of the low molecular weight organic solvents of the prior art" (column 4, lines 15-17).

Thus, it is clear that Gertzman goes to great lengths to distance the compositions described therein from the teachings of O'Leary, which utilize a low molecular weight organic carrier component. In light of this clear teaching away from O'Leary, there would be no motivation to combine the teachings of Gertzman with the O'Leary reference in the manner contemplated by the Examiner. For this additional reason, Applicants respectfully request that the Board overturn the sole rejection or record.

In the Advisory Action, the Examiner suggests that the teaching away of Gertzman is limited to glycerol-based carriers and notes that O'Leary discloses other types of carriers. However, as indicated above, Gertzman teaches away from all low molecular weight organic solvents, not just glycerol. O'Leary clearly suggests use of polyhydroxy compounds derived from "low molecular weight carboxylic acids" (column 3, lines 42-49). Thus, the teaching away in Gertzman is certainly more encompassing that glycerol and, in fact, is similar in scope to the liquid component of O'Leary.

8. ***Claims Appendix***

An appendix containing a copy of the claims involved in the appeal is attached.

9. ***Evidence Appendix***

No evidence has been submitted to the Examiner or relied upon by the Appellant.

10. ***Related Proceedings Appendix***

There are no decisions by a court or the Board in related proceedings.

CONCLUSION

In view of the foregoing arguments, Appellant respectfully submits that Claims 2, 3, 12-21, and 35-38 are patentable over the cited references. A decision from the Board of Patent Appeals and Interferences reversing the final rejection of the pending claims is therefore earnestly solicited.

Respectfully submitted,

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Tracey S. Wright

CLAIMS APPENDIX

2. (Previously Presented) A bone graft substitute composition comprising:

(a) calcium sulfate;

(b) a mixing solution;

(c) a cellulose derivative; and

(d) demineralized bone.

3. (Previously Presented) The bone graft substitute composition of claim 2, comprising approximately 40% demineralized bone matrix by dry weight.

12. (Previously Presented) A bone graft substitute composition comprising:

(a) approximately 80-120 parts medical grade calcium sulfate hemihydrate by weight;

(b) approximately 21-250 parts sterile water by weight;

(c) approximately 1-40 parts carboxymethylcellulose by weight; and

(d) approximately 10-100 parts demineralized bone matrix by weight.

13. (Previously Presented) The bone graft substitute composition of claim 2, wherein the mixing solution is selected from a group consisting of sterile water, an inorganic salt, and a cationic surface active agent.

14. (Previously Presented) The bone graft substitute composition of claim 13, wherein the cationic surface agent is selected from a group consisting of sodium chloride, phosphate buffered saline, potassium chloride, sodium sulfate, ammonium sulfate, ammonium acetate, and sodium acetate.

15. (Previously Presented) The bone graft substitute composition of claim 2, wherein the mixing solution comprises sterile water.

16. (Previously Presented) The bone graft substitute composition of claim 2, wherein the cellulose derivative is selected from a group consisting of sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, ethylcellulose, hydroxyethylcellulose and cellulose acetate butyrate.

17. (Previously Presented) The bone graft substitute composition of claim 2, wherein the cellulose derivative comprises carboxymethylcellulose.

18. (Previously Presented) The bone graft substitute composition of claim 2, wherein the calcium sulfate comprises calcium sulfate hemihydrate.

19. (Previously Presented) The bone graft substitute composition of claim 2, wherein the calcium sulfate comprises calcium sulfate hemihydrate, the mixing solution comprises sterile water, and the plasticizing substance comprises carboxymethylcellulose.

20. (Previously Presented) The bone graft substitute composition of claim 19, comprising approximately 100 parts calcium sulfate hemihydrate by weight, approximately 11.1 parts carboxymethylcellulose by weight, approximately 162 parts water by weight, and approximately 69.4 parts demineralized bone matrix by weight.

21. (Previously Presented) The bone graft substitute composition of any one of claims 2, 3, and 12-20, further comprising a bone allograft.

35. (Previously Presented) A method of making a bone graft substitute composition, the method comprising: providing a first composition comprising calcium sulfate, a cellulose derivative and demineralized bone matrix; and contacting the first composition with a mixing solution to form the bone graft substitute composition.

36. (Previously Presented) The method of claim 35, wherein the first composition further comprises a bone allograft.

37. (Previously Presented) The method of claim 35, further comprising forming the bone graft substitute composition into a putty.

38. (Previously Presented) The method of claim 35, wherein the calcium sulfate comprises calcium sulfate hemihydrate, the cellulose derivative comprises carboxymethylcellulose, and the mixing solution comprises sterile water.

EVIDENCE APPENDIX

No evidence has been submitted to the Examiner or relied upon by the Appellant.

RELATED PROCEEDINGS APPENDIX

There are no decisions by a court or the Board in related proceedings.